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25 November 2004

BY FAX TO: 00-4989-2399-4465
FROM: 020-7430 7600 - 17 PAGE(S)
CONFIRMATION BY COURIER

Dear Sirs,

International Patent Application No. PCT/GB04/002678
In the name of Pepharm R & D Limited
Representative's Ref: SCB/MPS/P72471WO00

In response to the Combined International Search Report and Written Opinion dated 30 September 2004 I hereby request International Preliminary Examination of the above referenced application. In this regard I enclose debit order No. L4877/P72471WO00 in respect of the Examination and Handling fees. I also enclose a full response to the Written Opinion and respectfully request that a further Written Opinion is issued prior to the issuance of the International Preliminary Report on Patentability (Chapter II) which takes into account the amendments and arguments offered.

Explanation of Amendments Made Under Article 34 PCT

The original claims of the above application have been amended. These amendments are made without prejudice to the possibility of reinstating the subject matter of these claims during further prosecution, including in the national phases. Where there were originally 29 claims, there are now 19 claims following amendment. Claims 1, 2, 7, 9, 10, 18, 19, 25, 26, 29 have been deleted and the remaining claims have been amended and renumbered without addition of any new claims. The amendments are shown in the enclosed marked up version of the claims for the assistance of the Examiner.

Response to Written Opinion of the ISA

The objections based on the cited references are addressed in turn below under the criteria of novelty, inventive step and industrial applicability.

Novelty

The objected claims directed to the tripeptide Tyrosyl-Seryl-Valine (hereinafter referred to as YSV) have all been amended so that they all now specify an isolated or purified peptide "consisting of" the tripeptide YSV. Claims objected to due to the wording "comprising" or "consisting essentially of" the tripeptide have been deleted. As such, the examiner's objections to Claims 1-4, 6, 7, 9, 19, 25, 26, 28, and 29 are moot.

D1

The objection raised by the Examiner that claims 2, 4, 6, 19, 26 and 28 are not novel over D1 has been addressed by the amendment and is now moot because D1 does not disclose the tripeptide YSV. The issue of the same activities between the tripeptides of D1 and the present application (YSV, YSL and YSP) is addressed under the heading of Inventive step below.

The examiner considers the tripeptides YSL and YSP of D1 to represent peptides "consisting essentially of the tripeptide Tyrosyl-Seryl-Valine". As defined in the present specification under the section "Detailed Description of the Preferred Embodiment" (8th paragraph), see page 12, the terminology "consisting essentially of" refers to "a peptide or polypeptide which includes the amino acid sequence of the YSV peptide or one of its functional derivatives along with additional amino acids at the carboxyl and/or amino terminal ends and which maintains the activity of said peptides provided herein."

By this definition, YSV does not encompass YSL or YSP of D1 as YSL or YSP do not have amino acid residues which are additional to YSV. However, as objected claims incorporating the terminology "consisting essentially of YSV" have been deleted, this point is moot.

D2

The examiner is of the opinion that the peptide YSVT is disclosed in D2 (WO 02/087505). The abstract, cited claims and paragraphs refer to the putative application of BCA polynucleotides, polypeptides and antagonists for the prevention or treatment of cancer, particularly breast cancer.

The objected Claims 1, 2, 4, 6, 7, 9, 25, 26, 28 and 29 were originally directed to peptides "comprising" or "consisting essentially of" YSV. These claims have been amended by deletion and the objection is, therefore, accordingly addressed. The amended claims render the present invention novel over D2.

D3

D3 relates to a synthesized pool of a highly complex nature of which YSL and YSV are disclosed as being among its components. As the two segments disclosed in D3 have not been isolated or

purified such that they do not exist in their entirety, it is respectfully contended that D3 does not anticipate the present invention directed to the tripeptide YSV. However, the claimed invention has been restricted to consisting of the tripeptide YSV where objected, to address the objections to original Claims 1-4, 6 and 29 by the examiner with regards to D3.

Furthermore, the selection of the tripeptide YSV from a library of 125 different tripeptides (page 220 column 2 and Table 3) is neither taught nor suggested by document D3 and the surprising technical effects achieved by virtue of this selection cannot be predicted from D3. Accordingly, the present invention meets the criteria of PCT Article 33(2) for novelty.

With the amendments offered, it is respectfully contended that the present invention is novel over all of documents D1, D2 and D3.

Inventive Step

D1

The examiner has objected to Claims 5, 8 and 10 relating to the L optical isomer forms of the invention. The other issues regarding inventiveness of the YSV tripeptide are addressed below. Once the inventiveness of the invention over D1 has been addressed and accepted, it is believed that original Claims 5, 8 and 10 will also be allowed as the L-forms of the invention will naturally fall under the ambit of the allowed broader claims.

The examiner has stated that D1 discloses YSL and YSF which differ from YSV by only one amino acid residue and that it is obvious to arrive at YSV from D1. However, it must be borne in mind that D1 discloses 30 different peptides, of varying lengths, of which YSL and YSF are members. There is no teaching in document D1 that the YSL and YSF tripeptides should be selected for additional studies including modification of the amino acid sequence.

It is respectfully submitted that it is not obvious to one skilled in the art to arrive at YSV from either YSL or YSF as there are conservatively between 30 to 60 different tripeptides (depending on how the 20 amino acids may be categorized according to their functional classes for parallel substitution of the three amino acid residues) which could be generated by the skilled person. Despite YSL and YSV differing in only the last amino acid residue, it is not known which position's amino acid residue is to be substituted because there is nothing to suggest that the last amino acid residue should be the one which is substituted. The passage referred to by the Examiner does not teach one of skill in the art that a substitution should be made only to the last amino acid. With particular reference to YSF, it is clear that a V for F substitution would not be readily carried out by one of skill in the art with a reasonable expectation of success. Phenylalanine is an amino acid having an aromatic side chain which valine, of course, does not have. Thus, the generic disclosure of YSL and YSF does not obviously lead one of skill in the art to the specific example that is YSV. The path leading from YSL or YSF to YSV is not a one-way street where a person skilled in the art can travel without undue experimentation and with a reasonable expectation of success.

As discussed above, one of skill in the art would not have arrived at the YSV tripeptide claimed herein without the exercise of inventive activity. In addition to this, the present specification discloses that YSV has activities not possessed by YSL and YSF and therefore the YSV molecule represents a surprising technical effect not obviously derivable from the cited prior art. The surprising activities are neither taught nor suggested by D1 or any other cited document.

The accompanying Table 1 lists some of these unexpected differences and advantages of YSV. Please note that the last test on inhibition of human hepatocellular carcinoma BEL7402 cells represents additional data generated by the applicant that has not been previously disclosed in the present specification. However, it is also to be appreciated that the technical problem being solved is not altered by the inclusion of this experimental data and accordingly, this additional surprising technical effect can be taken into account for the assessment of inventive step.

Table 1

S/No	Test Done	YSL Data (D1)	YSV Data
1	Enhance cytotoxic activity of NK cells (*in vitro*)?	Positive	No statistical difference
2	Enhance synthesis of anti-SRBC antibody upon the antigenic challenge?	Positive	No statistical difference
3	Enhance phagocytotic activity of mononuclear phagocyte?	Positive	No statistical difference
4	Increase weight of the thymus gland?	Positive	No statistical difference
5	Enhance T lymphocyte transformation?	Negative	Positive
6	Effect on leukemia	No effect seen on prolonging the survival of mice transplanted with L1210 leukemia	Inhibited the growth of transplanted human leukemia K562 in mice
7	Effect on the development of transplanted B16 melanoma in mice	Negative	Positive
8	Effect on inhibiting the growth of human hepatocellular carcinoma BEL7402 cells (*in vitro*)	Positive	Positive; twice as effective as YSL

It can be seen from the first four tests (serial numbers 1-4) that YSL and YSV do not have similar effects despite differing in only the last amino acid residue. The last four tests (serial numbers 5-8) show that YSV provides a number of surprising technical advantages over the previously described YSL tripeptide.

With these arguments and additional information, it can be seen that it is not obvious to arrive at a tripeptide having the amino acid sequence YSV starting from D1. As such, it is submitted that the present invention as amended is both novel and inventive over the cited prior art documents.

Industrial Applicability

The Examiner's highlighting of the issue of industrial applicability as regards previous claims 14-17 and 21-24 among the Contracting States has been noted. Claims 21-24 have been amended to "Swiss type" first and second medical use claims which are routinely allowed before the European Patent Office for example (see new claims 13 - 17), while method claims 14-17 (now numbered as claims 9 - 12) remain unchanged for those Contracting States that allow such claims (such as, for example, the United States).

The claims in question as amended have industrial applicability in the PCT contracting states that do allow claims 14-17 and 21-24 as phrased.

Conclusion

In summary, the tripeptide YSV *per se* has not been disclosed in the cited references and is hence novel. YSV possesses surprising technical effects and activities that are not obviously derivable from the prior art of record. Taken together, it is respectfully contended that the present application relating to the tripeptide YSV, with its claims as amended, describes an invention which is novel and inventive over D1, D2 and D3, and has industrial applicability.

I look forward to receiving a further Written Opinion in due course. If the amount listed on the enclosed debit order in respect of the fees for International Preliminary Examination is incorrect you are hereby authorized to deposit the necessary amount from our deposit account having the number 2805 0034.

Yours faithfully,

BALDOCK; Sharon Claire
Authorised Representative

Enclosure

595891: MPS: FP

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ _____

COPY

PCT DEMAND

CHAPTER II

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty.

For International Preliminary Examining Authority use only	
Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference SCB/MPS/P72471WO00
International application No. PCT/GB04/002678	International filing date *(day/month/year)* 22 June 2004	(Earliest) Priority date *(day/month/year)* 26 June 2003
Title of invention Biologically Active Peptide Comprising Tyrosyl-Seryl-Valine (YSV)		

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*	Telephone No.
Pepharm R & D Limited Room 1404, 14th Floor, Kodak House II, No. 39 Healthy Street East, North Point, Hong Kong, China.	Facsimile No.
	Teleprinter No.
	Applicant's registration No. with the Office

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
CN	CN

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

☐ Further applicants are indicated on a continuation sheet.

International application No.
PCT/GB04/002678

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative

and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.

☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

BALDOCK; Sharon Claire
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Teleprinter No.

Agent's registration No. with the Office

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

☐ the international application as originally filed

the description ☒ as originally filed
☐ as amended under Article 34

the claims ☐ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☒ as amended under Article 34

the drawings ☒ as originally filed
☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of the applicable time limit under Rule 69.1(d).

4. ☒ The applicant expressly wishes the international preliminary examination to start earlier than at the expiration of the applicable time limit under Rule 54*bis*.1(a).

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: ENGLISH

☒ which is the language in which the international application was filed.
☐ which is the language of a translation furnished for the purposes of international search.
☐ which is the language of publication of the international application.
☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The filing of this demand constitutes the election of all Contracting States which are designated and are bound by Chapter II of the PCT.

Sheet No. . 3

International application No.
PCT/GB04/002678

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

			For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:	sheets	☐	☐
2. amendments under Article 34	:	3 sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:	sheets	☐	☐
5. letter	:	5 sheets	☐	☐
6. other *(specify)*	:	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ original separate power of attorney
3. ☐ original general power of attorney
4. ☐ copy of general power of attorney; reference number, if any:
5. ☐ statement explaining lack of signature
6. ☐ sequence listing in computer readable form
7. ☐ tables in computer readable form related to a sequence listing
8. ☒ other *(specify)*: Debit Order No. L4877/P72471WO00

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

BALDOCK, Sharon Claire
Chartered UK Patent Attorney/European Patent Attorney
Boult Wade Tennant

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.
   ☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the time limit of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.
6. ☐ The date of receipt of the demand is AFTER the expiration of the time limit under Rule 54*bis*.1(a) and item 7 or 8, below, does not apply.
7. ☐ The date of receipt of the demand is WITHIN the time limit under Rule 54*bis*.1(a) as extended by virtue of Rule 80.5.
8. ☐ Although the date of receipt of the demand is after the expiration of the time limit under Rule 54*bis*.1(a), the delay in arrival is EXCUSED pursuant to Rule 82.

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Demand received from IPEA on:

CHAPTER II

PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/GB04/002678	For International Preliminary Examining Authority use only
Applicant's or agent's file reference SCB/MPS/P72471WO00	Date stamp of the IPEA

Applicant
Pepharm R & D Limited

CALCULATION OF PRESCRIBED FEES

1. Preliminary examination fee	1530 P	
2. Handling fee *(Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)*	129 H	
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	Euros 1659 TOTAL	

MODE OF PAYMENT

- ☐ authorization to charge deposit account with the IPEA (see below)
- ☐ cheque
- ☐ postal money order
- ☐ bank draft
- ☐ cash
- ☐ revenue stamps
- ☐ coupons
- ☒ other *(specify)*: Debit Order No. L4877/P72471WO00

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT

(This mode of payment may not be available at all IPEAs)

IPEA/ _____

☐ Authorization to charge the total fees indicated above.

☐ *(This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)* Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.

Deposit Account No.: _____

Date: _____

Name: _____

Signature: _____

See Notes to the fee calculation sheet

WHAT IS CLAIMED IS:

1. An isolated or purified peptide consisting of the tripeptide Tyrosyl-Seryl-valine.

2. The peptide of Claim 1 wherein said peptide has an activity selected from the group consisting of modulation of an immune response, stimulation of T lymphocyte transformation, modulation of a cell proliferative disorder, modulation of the growth of a cancer, modulation of the growth of a liver cancer, modulation of the growth of leukemia cells, modulation of the growth of a cervical cancer, modulation of the growth of a lung cancer and the modulation of the growth of a melanoma.

3. A peptide according to Claim 1 wherein said peptide is the tripeptide L-Tyrosyl-L-seryl-L-valine.

4. A peptide according to any of the Claims 1-3 wherein said peptide is in a substantially pure form.

5. A pharmaceutical composition comprising the tripeptide L-Tyrosyl-L-seryl-L-valine.

6. A pharmaceutical composition comprising a polypeptide consisting of the tripeptide Tyrosyl-seryl-valine.

7. A pharmaceutical composition according to Claim 6 comprising the tripeptide L-Tyrosyl-L-seryl-L-valine.

8. A method of making a pharmaceutical composition comprising providing the tripeptide Tyrosyl-seryl-valine and

mixing said tripeptide with a pharmaceutically acceptable carrier.

9. A method of reducing the effects of a human disease comprising administering a pharmaceutically effective dose of the tripeptide Tyrosyl-seryl-valine to a human.

10. The method of Claim 9, wherein said human suffers from a disease selected from the group consisting of a condition whose effects can be reduced by stimulating T lymphocyte transformation and a cell proliferative disorder.

11. The method of Claim 10, wherein said cell proliferative disorder is cancer.

12. The method of Claim 11, wherein said cancer is selected from the group consisting of liver cancer, leukemia, lung cancer, melanoma and cervical cancer.

13. A tripeptide consisting of Tyrosyl-seryl-valine for use in the treatment of a disorder.

14. The use according to Claim 13, wherein said disorder is a cell proliferative disorder.

15. The use according to Claim 14, wherein said cell proliferative disorder is cancer.

16. The use according to Claim 15, wherein said cancer is selected from the group consisting of liver cancer, leukemia, lung cancer, melanoma and cervical cancer.

17. The use according to Claim 13, wherein said disorder may be treated by modulation of the immune system.

18. The use of a peptide consisting of the tripeptide Tyrosyl-seryl-valine as a nutritional supplement.

19. A molecule comprising an enhanced derivative of the tripeptide Tyrosyl-seryl-valine, said enhanced derivative comprising an enhancement molecule operably linked to the tripeptide Tyrosyl-seryl-valine, said enhancement molecule enhancing the therapeutic effectiveness of said tripeptide.

WHAT IS CLAIMED IS:

~~1.An isolated or purified peptide comprising Tyrosyl-seryl-valine.~~

~~2.An isolated or purified peptide according to claim 1 consisting essentially of the tripeptide Tyrosyl-Seryl-valine.~~

~~3.~~1. An isolated or purified peptide ~~according to claim 1~~ consisting of the tripeptide Tyrosyl-Seryl-valine.

~~4.~~2. The peptide of Claim ~~1111~~2 wherein said peptide has an activity selected from the group consisting of modulation of an immune response, stimulation of T lymphocyte transformation, modulation of a cell proliferative disorder, modulation of the growth of a cancer, modulation of the growth of a liver cancer, modulation of the growth of leukemia cells, modulation of the growth of a cervical cancer, modulation of the growth of a lung cancer and the modulation of the growth of a melanoma.

~~5.~~3. A peptide according to ~~any of the~~ Claim~~s~~ ~~1-4~~ wherein said peptide is the tripeptide L-Tyrosyl-L-seryl-L-valine.

~~6.~~4. A peptide according to any of the Claims 1-~~3-4~~ wherein said peptide is in a substantially pure form.

~~7.A pharmaceutical composition comprising a polypeptide comprising the tripeptide Tyrosyl-seryl-valine.~~

~~8.~~5. A pharmaceutical composition ~~according to Claim 7~~ comprising the tripeptide L-Tyrosyl-L-seryl-L-valine.

~~9.A pharmaceutical composition comprising a polypeptide consisting essentially of the tripeptide Tyrosyl-seryl-valine.~~

~~10.A pharmaceutical composition according to Claim 9 comprising the tripeptide L-Tyrosyl-L-seryl-L-valine.~~

~~11.~~6. A pharmaceutical composition comprising a polypeptide consisting of the tripeptide Tyrosyl-seryl-valine.

~~12.~~7. A pharmaceutical composition according to Claim ~~11~~6 comprising the tripeptide L-Tyrosyl-L-seryl-L-valine.

~~13.~~8. A method of making a pharmaceutical composition comprising providing the tripeptide Tyrosyl-seryl-valine and mixing said tripeptide with a pharmaceutically acceptable carrier.

~~14.~~9. A method of reducing the effects of a human disease comprising administering a pharmaceutically effective dose of the tripeptide Tyrosyl-seryl-valine to a human.

~~15.~~10. The method of Claim ~~14~~ 9, wherein said human suffers from a disease selected from the group consisting of a condition whose effects can be reduced by stimulating T lymphocyte transformation and a cell proliferative disorder.

~~16.~~11. The method of Claim 10~~10101010150~~, wherein said cell proliferative disorder is cancer.

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